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SUMMARY WITH CRITICAL APPRAISAL

Nabilone for Non-Chemotherapy Associated Nausea and Vomiting and Weight Loss Due to Medical Conditions: A Review of Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

Nabilone is a synthetic drug belonging to the cannabinoid family. Cannabinoids are characterized by the active component delta-tetrahydrocannabinol.[1-3] Synthetic cannabinoids have been studied for the potential alleviation of symptoms for patients with a wide range of diseases including cancer, fibromyalgia, HIV/AIDS, inflammatory bowel disease, and patients undergoing palliative care.[2-4] Symptoms that may be managed using nabilone include chemotherapy-induced nausea and vomiting, neuropathic pain, disease-associated weight-loss, severe depressed mood, insomnia, multiple sclerosis associated spasticity and decreased quality of life.[2,3]

Despite the growing literature on the therapeutic benefits of synthetic cannabinoids, in Canada, nabilone remains approved exclusively for its use in the treatment of severe nausea and vomiting associated with cancer chemotherapy.[3] Nabilone is an oral medication with an onset of action of 60 to 90 minutes and duration of action of 8 to 12 hours.[3] Dosing for nabilone varies from 0.2 mg to 6.0 mg per day in divided doses.[3]

The purpose of this report is to evaluate the clinical effectiveness and guidelines for the use of nabilone for nausea and vomiting or weight-loss due to medical conditions not associated with chemotherapy.

This report serves as an update to CADTH's 2014 Rapid Response report.[5] This previous report reviewed four low quality studies and was unable to make any strong conclusions pertaining to the effectiveness of nabilone for non-chemotherapy nabilone for nausea or weight loss.

Research Questions

1. What is the clinical effectiveness of nabilone for the treatment of non-chemotherapy associated nausea and vomiting in adults and adolescents?
2. What is the clinical effectiveness of nabilone for the treatment of non-chemotherapy associated weight loss due to a medical condition in adults and adolescents?
3. What are the evidence-based guidelines associated with the use of nabilone for the treatment of non-chemotherapy associated nausea and vomiting in adults and adolescents?
4. What are the evidence-based guidelines associated with the use of nabilone for the treatment of non-chemotherapy associated weight loss due to a medical condition in adults and adolescents?

Key Findings

One low quality RCT provided evidence to suggest that at the dose used in the study nabilone was not effective in decreasing postoperative nausea and vomiting (PONV) in patients undergoing elective surgery.

One low quality guideline for the treatment of palliative nausea and vomiting suggested the use of nabilone when the etiology was unknown or related to anxiety.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including MEDLINE via Ovid, Embase via Ovid, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and June 26, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults and adolescents (age ≥ 13 years old) with non-chemotherapy associated nausea and vomiting Adults and adolescents (age ≥ 13 years old) with weight loss due to a medical condition (such as anorexia, HIV, etc.)
Intervention	Nabilone (Cesamet)
Comparator	Q1-2: Alternative active treatments; Placebo; No treatment Q3-4: No comparator
Outcomes	Q1-2: Clinical effectiveness (e.g., reduced nausea, reduced vomiting, change in weight) and safety (e.g., adverse events, abuse and misuse) Q3-4: Guidelines
Study Designs	Heath technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized control trials (RCT), non-RCTs, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014.

Critical Appraisal of Individual Studies

The included randomized study was critically appraised using the Downs and Black Checklist[6] and the guideline was assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described, narratively.

Summary of Evidence

Quantity of Research Available

A total of 133 citations were identified in the literature search. Following screening of titles and abstracts, 111 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. 16 potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 36 publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

One randomized control trial[8] (RCT) and one guideline[9] published between January 1, 2014 and June 26, 2017 met the inclusion criteria for this report. Detailed characteristics of the individual studies included in this report are provided in Appendix 2.

Study Design, Country of Origin, and Patient Population

Levin et al. published a double-blind, single-site, RCT in 2017.[8] This study aimed to assess the pragmatic use of nabilone to reduce PONV in 340 adult patients. Patients who were attending either the pre-anesthesia facility or admitted preoperatively for an elective surgery requiring general anesthesia were recruited from a single Canadian hospital. The final sample consisted entirely of female patients with an average age of 49.8 years for both the nabilone and placebo group.

In 2017, British Columbia's (B.C.) Guidelines and Protocols Advisory Committee (GPAC) released an updated clinical practice guideline for BC practitioners pertaining to pain and symptom management in adult patients undergoing palliative care for incurable cancer or advanced disease.[9] GPAC is comprised of members of the Doctors of BC and the Ministry of Health.[10] The Committee releases evidence-based clinical practice guidelines developed by a diverse working group.

Interventions and Comparators

The RCT assigned patients to receive a single treatment with 0.5 mg nabilone or placebo administered within three hours of the initiation of general anesthesia. This pragmatic trial allowed for the use of other anti-emetic or prophylactic medications.[8]

B.C.'s GPAC created specific recommendations for a number of symptoms associated with patients undergoing palliative care. The use of various medications for the management of nausea and vomiting were evaluated and organized into a framework to aid practitioners based on the etiology of the symptoms.[9]

Outcomes

Levin et al.'s RCT assessed nausea and vomiting (i.e., emesis, retching, or heaving) as the primary outcome using a modified PONV impact scale.[8] This scale assigned an absence of PONV a score of 0, incidence of nausea received a score of 1, and incidence of vomiting received a score of 2. PONV was identified if patients received a score above 0. The outcome was assessed at baseline and at the following intervals: 30, 60, 120, 180, 240, and 300 minutes or until the patient was discharged from the post-anesthesia care unit. Pain was assessed as a secondary outcome using an 11–point numerical rating scale

where “no pain” was assigned a score of 0, and “extreme pain” was assigned a score of 10. Intraoperative and postoperative use of morphine was recorded throughout the trial.

GPAC constructed frameworks for pain and symptom management for palliative care patients with incurable cancer or advanced disease.[9] Specific frameworks were constructed for the following symptoms: constipation, delirium, depression, dyspnea, fatigue and weakness, nausea and vomiting, and pain.

Summary of Critical Appraisal

The details of the critical appraisal for the RCT[8] and guideline[9] are provided in Appendix 3.

The RCT was clearly described.[8] The study outcomes to be assessed were clearly described in the Methods section. The source of study participants, relevant patient characteristics, and inclusion and exclusion criteria were provided. The interventions and dosing schedule for the treatment with nabilone and placebo were clearly described. The majority of the main confounding factors were evenly distributed between study groups. In addition to age, sex, weight, and height, patient use of other perioperative antiemetic medications were proportionally similar in terms of quantity and type of antiemetic medications. The main findings of the study were clearly described. The number of patients lost to follow-up was reported. Six patients in the placebo group were lost to follow-up due to five cancelled surgeries after taking the placebo, and one unexpected transfer to the intensive care unit after the surgery. There was no loss to follow-up in the nabilone group. Actual probability values were reported. Nabilone dosage and dosing schedule were not based on optimized information since nabilone for PONV has not been extensively studied. Patients in both the intervention (nabilone) group and placebo group were recruited from the same underlying population from a single hospital. The inclusion criteria included the patient to have three of four Apfel risk factors (i.e. female sex, non-smoker status, anticipated use of postoperative opioid, and previous PONV or motion sickness). This resulted in the selection of more female patients than male patients. The final study subjects included in the analysis was limited to female patients. These aspects of the study indicate limited external validity. In this study, all investigators, study coordinators, patients, clinicians and data analysts were blinded. Subjects were randomized using randomly varying block sizes and methods were used to ensure allocation concealment. These methods increased the internal validity of the study. Finally, a power calculation was provided and the study was sufficiently powered to detect a clinically significant (25%) reduction of PONV.

The overall objective and specific health questions covered by the guideline were described.[9,10] The guideline is clearly indicated for the use of British Columbia practitioners who treat patients undergoing palliative care for incurable cancer or advanced disease. The working group that developed the guideline included individuals from all relevant professional groups including general practitioners; specialists; content area experts; and a pharmacist. It was unclear if the preferences of the target palliative patient population were included in the development of this guideline. The methodology and evidence selection criteria are stated in the supplementary material. This additional material describes a rigorous process (including a systematic review) that is used in the development of each guideline. Each guideline is specific to B.C., and it is likely that the literature selection process reflects this. This indicates that the external validity of the guideline to a national population is limited. The health benefits, side effects, and risks have been considered in formulating the recommendations. The guideline has been externally peer-reviewed by experts in the field prior to publication. A procedure for updating the guideline is provided in

supplementary material. This guideline does not describe the associated strengths and limitations and fails to provide explicit links between the recommendations and the supporting evidence.

Summary of Findings

What is the clinical effectiveness of nabilone for the treatment of non-chemotherapy associated nausea and vomiting in adults and adolescents?

The RCT[8] examined the pragmatic use of oral nabilone compared to placebo in adult patients undergoing elective surgery under general anesthesia who were at risk of post-operative nausea and vomiting. This pragmatic trial permitted the use of other anti-emetic medications. The distribution of the quantity and type of other anti-emetic was similar between groups. This RCT determined that there was no difference in the incidence of PONV between the nabilone and placebo groups.

What is the clinical effectiveness of nabilone for the treatment of non–chemotherapy associated weight loss due to a medical condition in adults and adolescents?

No studies specific to non-chemotherapy associated weight loss due to a medical condition were identified.

Evidence-based guidelines associated with the use of nabilone for the treatment of non-chemotherapy associated nausea and vomiting in adults and adolescents?

B.C.'s GPAC developed a guideline for pain and symptom management in adult patients undergoing palliative care for incurable cancer or advanced disease. This guideline included a specific section pertaining to the management of nausea and vomiting. The nausea and vomiting-specific guideline recommended the selection of anti-nausea medication based on the etiology of the nausea and vomiting. For pharmacological management, the use of a "Nausea and Vomiting Management Algorithm" was recommended. Nabilone was recommended as one of five medications for the control of nausea and vomiting when the etiology was unknown. Nabilone was recommended as one two medications for the control of nausea and vomiting when the etiology was related to anxiety.

Evidence-based guidelines associated with the use of nabilone for the treatment of non-chemotherapy associated weight loss due to a medical condition in adults and adolescents?

No evidence-based guidelines were identified for the use of nabilone for non-chemotherapy associated weight loss.

Limitations

The quality of the RCT[8] was limited by a number of methodological issues. This study exclusively recruited patients from a single hospital in Ontario. The single-site methodology reduced the external validity of the study as patients at a single hospital are not representative of the diverse patient population across Canada. While this study was intended to represent all elective surgery patients undergoing general anesthesia, the study preferentially selected for female patients due to the inclusion criteria. One of the inclusion criteria required patients to have three of four Apfel risk factors for PONV (i.e. female sex, non-smoker status, anticipated use of postoperative opioid, and previous PONV or motion sickness) that resulted in female patients being preferentially selected for the study. While

some male patients were included in the initial sample, they were excluded for other reasons throughout the study resulting in a final sample exclusively composed of female patients. This criterion resulted in limiting the external validity of the study as the sample population was not generalizable to the target population. This study looked at off-label nabilone use thus, the dosage and dosing schedule was not based on optimized information. This inherently acts as a limitation to the study as it is not certain if the nabilone dose was biologically appropriate.

The quality of the guideline[9] was limited by a lack of specificity and methodological ambiguity. This guideline was a general guideline for pain and symptom (i.e. nausea and vomiting) management in adult patients undergoing palliative care for incurable cancer or advanced disease. The guideline recommends various drugs (i.e. nabilone) for the treatment of symptoms based on etiology, but provides very little detail and fails to specify the specific literature sources that inform each recommendation. The recommendation fails to include important information including dosing, and strengths and limitations of the guideline. While it is made clear in the supplementary material[10] that a variety of relevant professionals were consulted throughout the general process, it remains unclear which professionals were consulted in this specific guideline and if preferences of the target patient population were included.

Conclusions and Implications for Decision or Policy Making

The single-site RCT[9] found no difference in the incidence of PONV for patients using nabilone compared to placebo. This indicates that nabilone is not effective in reducing PONV at the dose used in the study. An additional RCT[2] that did not meet the inclusion criteria for this report determined that nabilone was not effective in decreasing nausea or treating weight loss in patients undergoing radiotherapy treatments for head and neck cancer. This study was excluded from the report due to the inclusion of a mixed population where some patients were receiving chemotherapy. Collectively, these studies suggest that nabilone may not be effective for the treatment of non-chemotherapy associated nausea and vomiting. These findings are not generalizable to the general population suffering from non-chemotherapy associated nausea and vomiting and are based on unoptimized nabilone doses. Further study in the form of high quality multi-site double-blind RCTs is needed to inform policy making. CADTH's previous 2014 report[5] included the review of a low-quality RCT and a low-quality cohort study. Both of these studies supported the use of nabilone for non-chemotherapy. However due to the low quality of evidence available at that time, conclusions pertaining to the effectiveness of nabilone were not made. Because of this, the findings of the 2014 Rapid Response report are not easily comparable to the current review.

Guidelines for the treatment of palliative nausea and vomiting suggested the use of nabilone when the etiology was unknown or related to anxiety. More specific guidelines pertaining to the use of nabilone for non-chemotherapy associated nausea and vomiting are required. A gap in the recent literature exists for studies and guidelines specific to non–chemotherapy associated weight loss due to a medical condition as our literature search yielded zero results; thus, further study is warranted.

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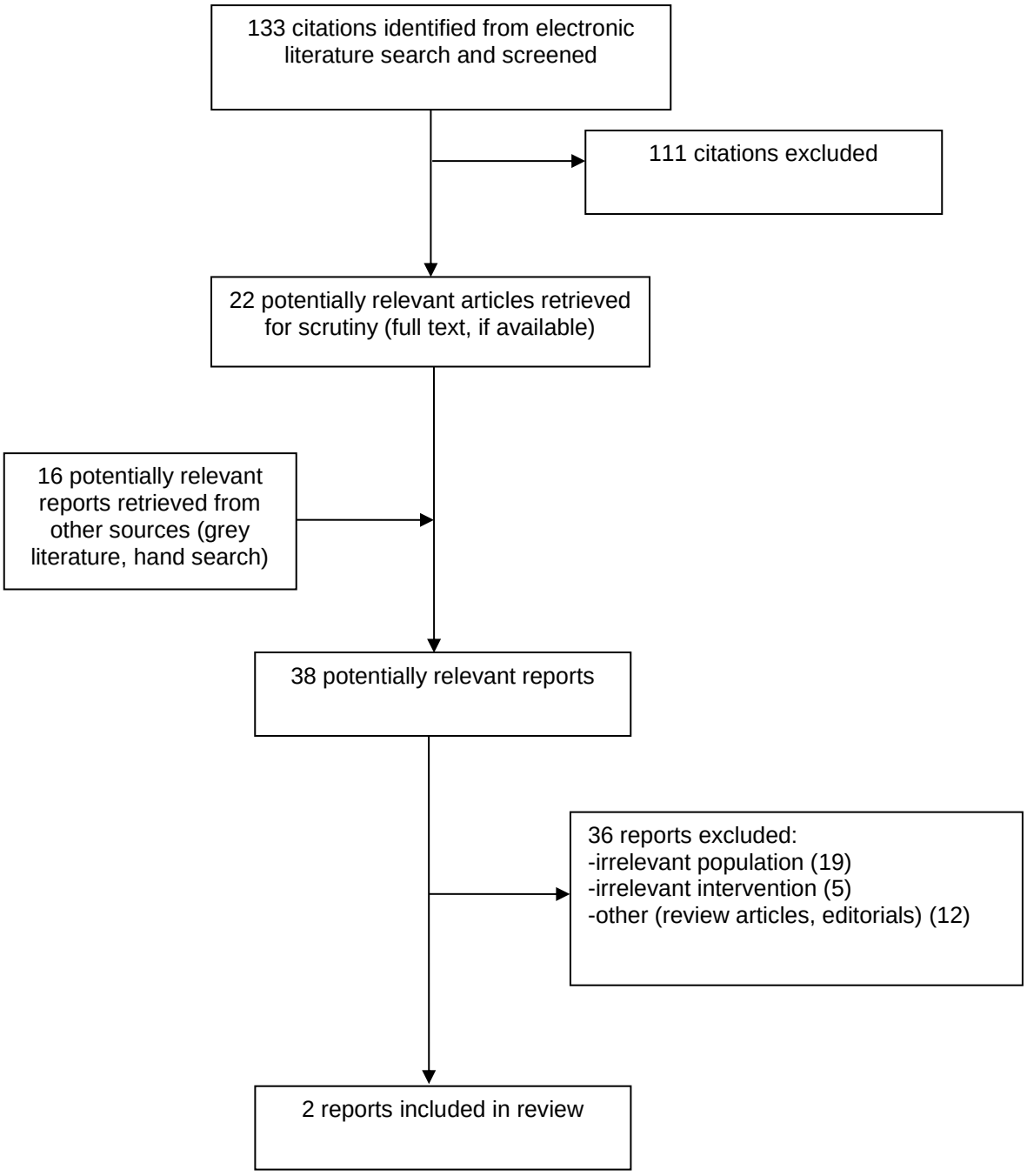
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Clinical Study

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Levin, 2017, Canada[8]	Double-blind, parallel group, pragmatic RCT, interval follow-up 300 minutes post-operation or until time of discharge	Patients (n=340) attending the paranesthesia facility or admitted to the hospital preoperatively for elective surgery aged 18 and above. Sex (%) Nabilone – 100 female Placebo – 100 female Age (mean) Nabilone – 49.8 Placebo – 49.8	Nabilone 0.5 mg administered within three hours prior to the induction of anesthesia. Use of other anti-emetics or prophylaxis was permitted.	Placebo was administered with the same procedure as the intervention. Use of other anti-emetics or prophylaxis was permitted.	Nausea and vomiting were assessed using a modified PONV scale. Pain was assessed using an 11-point NRS

RCT = randomized controlled trial; RT = radiotherapy; RC = radiochemotherapy; PONV = postoperative nausea and vomiting; NRS = numerical rating scale

Table 3: Characteristics of Included Guideline

First Author, Publication Year, Country	Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Guideline Validation
GPAC, 2017, Canada[9]	Recommendations for B.C. practitioners delivering high quality, appropriate care to patients undergoing palliative care for incurable cancer or advanced disease for pain and symptom management	A framework to select medication (i.e. anti-nausea medication based on the etiology of the nausea and vomiting	Anti-nausea medication for nausea and vomiting arising from the following sources: Gastroenterological, chemical, vestibular and motion-related, central nervous system, and cause unknown	The CPG is developed by a working group composed of general practitioners, specialists and other content area experts, and a pharmacist. The CPG is peer reviewed prior to publication.	GPAC is a joint committee between the Doctors of BC and the Ministry of Health

GPAC = Guidelines and Protocols Advisory Committee; B.C. = British Columbia; CPG = clinical practice guideline

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Randomized Controlled Trial using the Downs & Black Checklist

Strengths	Limitations
Levin,[8] 2017	
• Aim of study was provided • Study outcomes were described in Methods section • Source, relevant characteristics, and inclusion and exclusion criteria for patients were provided • Interventions for both groups were clearly described • Main study findings were clearly described • Patients lost to follow-up was reported • Probability values were reported • Even distribution of majority of confounding factors • Extensive blinding procedure followed • All patients recruited from the same underlying population • Subjects were randomized using randomly varying block sizes and allocation concealment procedures • Similar distribution of confounders between treatment groups • Power calculation provided; study sufficiently powered to detect clinically important effect	• Patients recruited from one hospital • Inclusion criteria preferentially selected for female patients • Nabilone dosage and dosing schedule not based on optimized information

Table 5: Strengths and Limitations of Guidelines using AGREE II

Strengths	Limitations
GPAC,[9] 2017	
• Overall objective and specific health questions were described • Target population is specifically described • Developed by all relevant professional groups (general practitioners, specialists, content area experts, pharmacist) • Standardized, systematic methods were used to search for evidence • Criteria for selecting evidence was clearly described in supplementary material • General method for formulating recommendation was described in supplementary material • Health benefits, side effects, and risks were considered in formulating the recommendations • Guideline was externally peer-reviewed by experts in the field prior to publication • A procedure for updating the guideline provided in supplementary material	• Unclear if preferences of the target patient population were included • Strengths and limitations specific to the guideline were not clearly described • The explicit link between recommendations supporting evidence was not clearly stated • Recommendations are general

GPAC = Guidelines and Protocols Advisory Committee; B.C. = British Columbia

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Levin,[8] 2017	
There was no difference in the incidence of patients PONV (RR = 0.98; 95% CI = 0.89 to 1.11; P = 0.99), where PONV occurred in 20.9% of patients in the nabilone group, and 21.4% in the placebo group. There were no differences in postoperative pain scores (P = 0.70) or postoperative opioid consumption (P = 0.85).	"Oral nabilone 0.5 mg given as a single dose prior to surgery is ineffective in reducing PONV." p.385
GPAC,[9] 2017	
Guideline: Select anti-nausea medication based on the etiology of the nausea and vomiting. Assessment for nausea and vomiting: • Identify and discontinue medications that may be the cause • Further assessment may be required (i.e., lab tests, imaging) • Symptom control may require rehydration using hypodermoclysis Management for nausea and vomiting: • Non–pharmacological: modifications to diet and environment, relaxation, oral hygiene, acupressure • Pharmacological: match treatment to cause • Consider pre-emptive use of anti-nausea medication in opioid-native patients	Select anti-nausea medication based on the etiology of the nausea and vomiting. For pharmacological management use the "Nausea and Vomiting Management Algorithm". Nabilone recommended for the control of nausea and vomiting in palliative patients with incurable cancer or advanced disease when the etiology of nausea and vomiting is unknown or related to anxiety.

PONV = postoperative nausea and vomiting; RR = relative risk; 95% CI = 95% confidence interval; P = p-value